

**REMARKS**

Favorable reconsideration is respectfully requested in view of the following remarks.

**I. CLAIM STATUS & AMENDMENTS**

Claims 24-35 have been examined on the merits and stand rejected.

**II. OBJECTION TO THE CLAIMS**

Claims 30-35 were objected for being drawn to the same method as claims 24-29, respectively. See page 2 of the Office Action.

This objection is respectfully traversed as claims 30-35 are not drawn to the same method of claims 24-29. The two sets of claims differ in scope. Specifically, claims 24-29 are directed to preventing recurrence of liver cancer, whereas claims 30-35 are directed to preventing recurrence of cancer in general. As such, the claims are not substantial duplicates of each other. In fact, this difference in claim scope was acknowledged on pages 2-3 of the Office Action of March 13, 2003.

For this reason, the objection is untenable and should be withdrawn.

**III. OBVIOUSNESS REJECTION**

Claims 24-35 were rejected under 35 U.S.C. § 103(a), as obvious over Sekine et al., Human Cell, Vol. 7, No. 3, pp. 121-124 (1994) in view of Sasaki et al., J. of HBP Surgery, Vol. 5, pp. 14-17 (1998). See pages 3-6 of the Office Action.

This rejection is respectfully traversed.

The claimed invention relates to methods for preventing recurrence of liver cancer and cancer in general by administering activated lymphocytes in combination with a surgical procedure to prevent the recurrence of the cancer for at least five years.

Sekine fails to disclose a method resulting in the prevention of recurrence of liver cancer or cancer in general for at least five years. This is acknowledged in the paragraph bridging pages

2-3 of the Office Action, wherein it is indicated that “Sekine et al. do not teach prevention of recurrence of cancer for five years.” Furthermore, in the 10<sup>th</sup> line from the bottom of page 122 of Sekine, it is disclosed that significant differences were shown in recurrence rate among the groups from 6 months to 17 months post-therapy, whereas FIG. 3, which shows the recurrent-free survival, proves that no significant difference of the groups thereafter was recognized. Therefore, it is respectfully submitted that the claimed method of preventing recurrence of liver cancer and cancer in general by administering activated lymphocytes in combination with a surgical procedure to prevent the recurrence of the cancer for at least five years could not have been suggested from the teachings in Sekine. See the Table below.

	Sekine, “Human Cell”		Present Invention
	Reoccurrence at 2 years	2-year event-free survival rate	5-year event-free survival rate
Lymphocyte-administered group	26.5% (13/49)	62% (one fatal case)	35%
Controls (non-administered group)	42.3% (22/52)	51% (six fatal cases)	21%

Sasaki fails to remedy the deficiencies of Sekine.

Sasaki is relied upon for disclosing the survival rate for liver cancer patients following the surgical procedure of hepatic resection. Sasaki fails to disclose or suggest administering activated lymphocytes in combination with a surgical procedure to prevent the recurrence of the cancer for at least five years. Based on teachings of Sasaki, the Office takes the position that cancer patients are expected to live at least five years following a surgical procedure for removal of the cancer. See the sentence bridging pages 5-6.

However, regarding the alleged 5-year survival rate after hepatic resection, it appears that the Office has confused the terms “recurrent--free survival (RFS)” and “over-all survival (OS)”.

The survival curve in RFS drops with recurrence during a period of observation, whereas the survival curve in OS is invariable, but drops with fatal cases.

In other words, the survival rate in the present invention is the recurrent-free survival (RFS), but the survival rate in Sasaki is the over-all survival (OS). Thus, the present invention is fundamentally distinct from the disclosure in Sasaki. As such, the claimed invention could not have been suggested from the teaching in Sasaki when taken with Sekine.

Furthermore, regarding the effectiveness of activated-lymphocyte therapy, adoptive immunotherapy such as LAK therapy and TIL therapy brings about only an antitumor effect partially on specific cancers in comparison with chemical therapy and irradiation therapy (Osband et. al., Lancet, 10:335 (1990)). Likewise, as disclosed at the top of page 2 of the specification, the efficacy of preventing recurrence of cancer and the antitumor activity of administered activated LAK cells lasted only for a short period of about two years.

The Office's position regarding the expected 5-year survival is inconsistent with the high recurrence rates disclosed in Sekine. As argued in the previous response, Sekine discloses that the recurrence rate for liver cancer is 33% in the first year, 57% in the second year, 70% in the third year, and that no effective preventative method is known. In this sense, Sekine teaches away from the claimed method of prevention for 5 years. As such, based on the teachings of Sekine and the general knowledge in the art, no reasonable expectation of success existed at the time of the publication of Sekine for the prevention of recurrence of liver cancer or cancer in general for five years.

In contrast, the Applicants first discovered that activated lymphocytes can surprisingly prevent cancer recurrence in liver cancer patients for five years after treatment.

Thus, notwithstanding that the claimed invention is not obvious over the cited references, the data of the instant invention amounts to surprising and unexpected results over the teachings of the cited references. As demonstrated at page 13, lines 1-7 of the specification, the efficacy of the instant invention for the prevention of cancer is at least five years. Five years far exceeds the

two years disclosed in Sekine. Prevention of recurrence for five years is unexpected in view of the intractable nature of cancer as discussed in the previous responses.

Finally, the effectiveness of the activated lymphocytes for cancers other than liver cancer was confirmed through a clinical study conducted by one of the inventors of this invention, Mr. Sekine. The clinical study was conducted by extirpating all cancerous parts while scanning with MRI and providing glioblastoma patients treated with ordinary chemical therapy and irradiation therapy with medical treatment using activated lymphocytes according to the present invention once monthly for 60 months at the maximum. As a consequence, three of five patients have enjoyed being free from recurrence of cancer for 132 months, 120 months and 45 months, respectively. The remaining two patients suffered a relapse in postoperative at 24<sup>th</sup> month and 8<sup>th</sup> month, respectively. However, thereafter, these patients stayed for further 48 months and 45 months through weekly or biweekly administration of activated lymphocytes. Particularly, the patient who acted up in postoperative 24<sup>th</sup> month developed rapidly recurrent cancer following discontinuation of administration of activated lymphocytes in postoperative 39<sup>th</sup> month, and subsequently died in 48<sup>th</sup> month.

In general, a historical control treated with ordinary chemical therapy and irradiation therapy will survive for one year to one-and-a-half years postoperatively. See the "Background" section on pages 2-3 of the disclosure. In contrast, the activated lymphocytes according to the present invention could dominantly prevent glioblastoma recurrence.

Therefore, the rejection of claims 24-35 under 35 U.S.C. § 103(a) is untenable and should be withdrawn.

Attorney Docket No.: 2001\_1248  
Application No.: 09/944,360  
July 5, 2005

**CONCLUSION**

In view of the foregoing amendments and remarks, it is respectfully submitted that the application is in condition for allowance and early notice to that effect is hereby requested.

If the Examiner has any comments or proposals for expediting prosecution, please contact the undersigned attorney at the telephone number below.

Respectfully submitted,

Teruaki SEKINE et al.

By: Warren M. Cheek, Jr.  
Warren M. Cheek, Jr.  
Registration No. 33,367  
Attorney for Applicant

WMC/JFW/wrs  
Washington, D.C. 20006-1021  
Telephone (202) 721-8200  
Facsimile (202) 721-8250  
July 5, 2005